PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 October 2000 (18.10.00)	
International application No. PCT/CA00/00246	**Applicant's or agent's file reference** 12926-2PCT
International filing date (day/month/year) 09 March 2000 (09.03.00)	**Priority date** (day/month/year) 15 March 1999 (15.03.99)
Applicant LEYLAND-JONES, Brian et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 August 2000 (29.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
12926-2PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00246	09/03/2000	15/03/1999
Applicant		
LEYLAND-JONES, Brian et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00246

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 16

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 - 16

   Method, ELISA and kit for determining CYP 1A2 phenotype, based on the determination of the molar ratio between caffeine and selected metabolites thereof.

2. Claims: 17 - 32

   Method, ELISA and kit for determining NAT1 phenotype, based on the determination of the molar ratio between p-aminosalicylic acid and selected metabolites thereof.

3. Claims: 33 - 48

   Method, ELISA and kit for determining CYP 2D6 phenotype, based on the determination of the molar ratio between dextromethorphan and selected metabolites thereof.

4. Claims: 49 - 64

   Method, ELISA and kit for determining CYP 2E1 phenotype, based on the determination of the molar ratio between chlorzoxazone and selected metabolites thereof.

5. Claims: 65 - 80

   Method, ELISA and kit for determining CYP 3A4 phenotype, based on the determination of the molar ratio between dextromethorphan and selected metabolites thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00246

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/53 G01N33/543 C07D473/08 C07D473/10 C07D473/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WONG P ET AL: "Synthesis of caffeine metabolites derivatives for measuring CYP1A3 activity by ELISA." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 53 XP002144104 90th Annual Meeting of the American Association for Cancer Research;Philadelphia, Pennsylvania, USA; April 10-14, 1999, March, 1999 ISSN: 0197-016X abstract --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2000	13. 11. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, M

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 04757 A (UNIV TEXAS) 16 February 1995 (1995-02-16) page 5, line 7-13 page 5, line 29 -page 6, line 13 page 9, line 9-29 page 11, line 17-23 page 12, line 5-15 claims 9,11,13,14,16,18-29,37	1-16
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1991 TANG B-K ET AL: "CAFFEINE AS A METABOLIC PROBE VALIDATION OF ITS USE FOR ACETYLATOR PHENOTYPING" Database accession no. PREV199192067910 XP002144105 cited in the application abstract & CLINICAL PHARMACOLOGY & THERAPEUTICS, vol. 49, no. 6, 1991, pages 648-657, ISSN: 0009-9236	1-16
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1990 KILBANE A J ET AL: "HUMAN N-ACETYLATION GENOTYPE DETERMINATION WITH URINARY CAFFEINE METABOLITES" Database accession no. PREV199090015389 XP002144106 cited in the application abstract & CLINICAL PHARMACOLOGY & THERAPEUTICS, vol. 47, no. 4, 1990, pages 470-477, ISSN: 0009-9236	1-16
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1998 (1998-05) MEACHER DIANNE M ET AL: "Analysis of NAT and CYPIA2 phenotypes and NAT2* genotype by capillary electrophoresis." Database accession no. PREV199800360878 XP002144107 cited in the application abstract & BIOMARKERS, vol. 3, no. 3, May 1998 (1998-05), pages 205-218, ISSN: 1354-750X	1-16

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International Application No
PCT/CA 00/00246

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 645 459 A (COOK DORN C ;PARKINSON ANDREW (US)) 29 March 1995 (1995-03-29) page 3, line 6,7 page 3, line 48 -page 4, line 55 claims 1-5	1-16
A	US 5 830 672 A (LEYLAND-JONES BRIAN ET AL) 3 November 1998 (1998-11-03) column 2, line 28-50 column 3, line 42-55 example 1 claim 5	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/00246

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9504757 A	16-02-1995	AU 7452094 A	28-02-1995
EP 0645459 A	29-03-1995	US 5478723 A	26-12-1995
US 5830672 A	03-11-1998	CA 2167330 A	01-08-1997

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
12926-2PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00246	09/03/2000	15/03/1999
International Patent Classification (IPC) or national classification and IPC G01N33/53		
Applicant LEYLAND-JONES, Brian et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/08/2000	12.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Goetz, M Telephone No. +49 89 2399 8697

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00246

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-56	as originally filed	

Claims, No.:

12-79	as originally filed	
1-11,80-95	with telefax of	09/04/2001

Drawings, sheets:

1/10-10/10	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 17 - 95.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 17 - 95.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1 - 16.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1 - 16
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1 - 16
Industrial applicability (IA)	Yes:	Claims 1 - 16
	No:	Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Since no International Search Report has been established neither for claims 17 - 80 as originally filed nor for claims 81 - 95 as filed with telefax dated 06/04/2001, only claims 1 - 16 form the basis for this Written Opinion.

Re Item IV

Lack of unity of invention

1. The IPEA agrees with the objection already put forward by the ISA as to lack of unity (Rule 13 PCT), the reasons for the objection being as follows:

Claims 1 - 16: Method, ELISA and kit for determining CYP 1A2 phenotype, based on the determination of the molar ratio between caffeine and selected metabolites thereof.

Claims 17 - 32: Method, ELISA and kit for determining NAT1 phenotype, based on the determination of the molar ratio between p-aminosalicylic acid and selected metabolites thereof.

Claims 33 - 48, 86, 87, 90, 91: Method, ELISA and kit for determining CYP 2D6 phenotype, based on the determination of the molar ratio between dextromethorphan and selected metabolites thereof; derivatives of dextromethorpan.

Claims 49 - 64, 88, 89: Method, ELISA and kit for determining CYP 2E1 phenotype, based on the determination of the molar ratio between chlorzoxazone and selected metabolites thereof; derivatives of chlorzoxazone.

Claims 65 - 82, 86, 87, 90, 91: Method, ELISA and kit for determining CYP 3A4 phenotype, based on the determination of the molar ratio between dextromethorphan and selected metabolites thereof; derivatives of dextromethorpan.

Claims 92, 93: Method of synthesizing caffeine and 1,7-dimethylxanthine derivatives according to Fig. 8.

Claims 94, 95: Method of synthesizing caffeine and 1,7-dimethyluric acid derivatives according to Fig. 9.

2. They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

   a) Each of the first five inventions relates to the determination of a unique selected phenotype represented by the assay of a unique analyte (CYP-1A2, NAT1, CYP-2D6, CYP-2E1 and CYP-3A4), each assay using its own unique set of detecting reagents such as antibodies and metabolites. Specific derivatives of the metabolites under consideration are also claimed.

   Hence, these five inventions are not a priori linked by a common technical concept so as to meet the requirements for unity (the fact that all phenotypes are determined by carrying out an ELISA is a trivial feature which does not render them unitary).

   b) The last two inventions relate to different particular synthetic pathways which have no common technical link with the group of the first five inventions.

R It m V

Reasoned statement under Art. 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: KILBANE et al., Clin. Pharmacology & Therapeutics 47, 1990 p. 470 - 477
   D2: TANG et al., Clin. Pharmacology & Therapeutics 49, 1991, p. 648 - 657
   D3: MEACHER et al., Biomarkers 3, 1998, p. 205 - 218
   D4: WO95/04757
   D5: US-A-5 830 672
   D6: Wong et al., Proceedings of the American Association for Cancer Research Annual Meeting Vol. 40, March 1999, p. 53

2. As also seen in the present description, page 21/lines 7 - 19, documents **D1**, **D2** and **D3** disclose that the CYP 1A2 phenotype has been determined by using the ratio 1,7-DMX + 1,7-DMU / 1,3,7-TMX (caffeine), but using other detection methods such as HPLC and CE.

   Claim 1 differs from **D1** - **D3** in that the detection of the caffeine metabolites is carried out by using an antibody-based detection method.

   The problem to be solved may therefore be regarded as the provision of an improved, easy-to-use method for the determination of the CYP 1A2 phenotype based on the molar ratio 1,7-DMX + 1,7-DMU / 1,3,7-TMX (caffeine). The solution offered in claim 1 resides in the provision of at least 3 different antibodies to caffeine and first and second caffeine metabolites.

2.1 Document **D4** discloses a method for the determination of an acetylator phenotype based on an ELISA method and a kit which uses or comprises at least 2 different monoclonal antibodies against an acetylated and a non-acetylated metabolite of an acetylizable drug (such as caffeine) in order to calculate a ratio of the said two metabolites; the acetylated metabolite is preferably AAMU and the non-acetylated metabolite is preferably 1-MX; the method, ELISA and kit according to **D4** is provided in order to replace HPLC-, GC- or MS-based methods

for the determination of the said ratio (see **D4**, page 5/lines 7 - 13, page 5/line 29 - page 6/line 13, page 9/lines 9 - 29, page 11/lines 17 - 23, page 12/lines 5 - 15, claims 9, 11, 13, 14, 16, 18 - 29 and 37).

The potential suitability of the method of **D4** for calculating the CYP 1A2 phenotype is mentioned expressis verbis in **D4**, page 22 / lines 20 - 23.

2.2. As monoclonal antibodies against selected caffeine metabolites have already been prepared in **D4**, a document addressing exactly the same technical problem as the present application, the skilled person, knowing about the importance of the ratio 1,7-DMX + 1,7-DMU / 1,3,7-TMX (caffeine) for determining the CYP 1A2 phenotype (documents **D1** - **D3**), would immediately consider the preparation of (monoclonal or polyclonal) antibodies against the 3 metabolites 1,7-DMX + 1,7-DMU and 1,3,7-TMX and use them in the same way as the inventors of D4 did; he/she would therefore arrive at the subject-matter of present claims 1, 2, 5 and 9 without the exercise of inventive skill.

2.3. Claims 1, 2, 5 and 9 do not therefore meet the requirements according to Art. 33(3) PCT.

2.4. Additional explanation: the Applicant argues that the preparation of the **D4** antibodies substantially differs from the antibodies as prepared in the framework of the presently claimed subject-matter. More particularly, the **D4** antibodies allegedly would not appear to be metabolite-specific, but to be cross-reactive between 1,7-dimethylxanthine and 1-methylxanthine. Hence, in the Applicant's view, the skilled person would not be tempted to use **D4** as a document contributing to the solution of the technical problem outlined above.

The IPEA is of the opinion that the Applicant misses the core of the objection raised under Art. 33(3) PCT against the claims.

Indeed, as explained above, **D4** aims at replacing known HPLC-, GC- or MS-based methods for the determination of a ratio of selected caffeine metabolites by an ELISA based method. **D4** shows the skilled person that antibodies against caffeine metabolites can be prepared without substantial difficulties.

Hence, the skilled person, being absolutely familiar with general techniques for the preparation of specific antibodies, and knowing about the importance of the ratio 1,7-DMX + 1,7-DMU / 1,3,7-TMX (caffeine) for determining the CYP 1A2 phenotype (documents **D1** - **D3**), would indeed consider to at least try the preparation of (monoclonal or polyclonal) antibodies against the 3 metabolites 1,7-DMX + 1,7-DMU and 1,3,7-TMX and use them in the same way as the inventors of **D4** did for their assay. He/she does not necessarily rely on the **D4** antibodies to be suitable for the assay system claimed in the present invention; it is sufficient that **D4** shows the direction in which further work should go.

The skilled person would therefore arrive at the subject-matter of present claims 1, 2, 5 and 9 without the exercise of inventive skill.

NB: It should be mentioned that the same approach for the replacement of complex methods such as HPLC or CE by immunoassays has already been used in the determination of the NAT2 phenotype, see **D5**, column 2/lines 28 - 50 and claim 5.

3. Claims 3, 4, 6 - 8 and 10 - 16 relate to commonly known preferred embodiments of the subject-matter recited in independent claims 1, 5 and 9 which do not involve an inventive step per se; also these claims cannot therefore be considered to meet the requirements according to Art. 33(3) PCT.

4. It appears that **D6** has been published between the presently claimed priority date and the filing date; hence, should the present priority be invalid, **D6** would appear to be detrimental to the novelty and/or inventive step of each one of claims 1 - 16.

Re Item VII

Certain defects in the international application

Contrary to Rule 5.1 (a)(ii) PCT, the teaching provided by document D4 has not at least briefly been discussed in the description.

R Item VIII

Certain observations on the international application

The indication of molar ratio values such as "4" and "12" in claims 1, 5 and 9 would appear to be meaningless without the indication of what the said ratios are composed of; in order to comply with Art. 6 PCT, it would appear to be necessary to include in the said claims the said composition (with the current claim wording, both 1,7-DMX + 1,7-DMU / 1,3,7-TMX, or 1,3,7-TMX / 1,7-DMX + 1,7-DMU are conceivable).

WHAT IS CLAIMED IS:

1. A method of determining CYP 1A2 phenotype of an individual which comprises measuring molar ratio of caffeine and first and second different metabolites of caffeine in a biological sample of said individual after drinking a caffeine solution with at least three antibodies, each specific to caffeine or a different metabolite of caffeine, wherein a molar ratio of 4 is indicative of slow intermediate and of 12 is indicative of fast CYP 1A2 metabolizers; and whereby said molar ratio is indicative of a CYP 1A2 phenotype of said individual.

2. The method of claim 1, wherein said first caffeine metabolite is selected from the group consisting of 1,7-dimethylxanthine (1,7 DMX), and those illustrated in Fig. 3; wherein said second caffeine metabolite is selected from the group consisting of 1,7-dimethyluric acid (1,7 DMU), and those illustrated in Fig. 4; and wherein said third metabolite is selected from the group consisting of 1,3,7-trimethylxanthine (caffeine) and those illustrated in Fig. 2.

3. The method of claim 2, wherein said biological sample is urine sample.

4. The method of claim 3, wherein said determined CYP 1A2 phenotype of said individual allows physician to predict susceptibility to carcinogen induced disease and/or to individualize drug treatments.

5. A competitive enzyme linked immunosorbent assay (ELISA) method for determining CYP 1A2 phenotype, which comprises using at least three antibodies each specific to caffeine or a different metabolite of caffeine to measure their molar ratio in biological sample of an individual after drinking a caffeine solution; wherein a molar ratio of 4 is indicative of slow intermediate and of 12 is indicative of fast CYP 1A2 metabolizers; and whereby said molar ratio is indicative of a CYP 1A2 phenotype of said individual.

6. The ELISA method of claim 5, wherein said first caffeine metabolite is selected from the group consisting of 1,7-dimethylxanthine (1,7 DMX), and those illustrated in Fig. 3; wherein said second caffeine metabolite is selected from the group consisting of 1,7-dimethyluric acid (1,7 DMU), and those illustrated in Fig. 4; and wherein said third metabolite is selected from the group consisting of 1,3,7-trimethylxanthine (caffeine) and those illustrated in Fig. 2.

7. The ELISA method of claim 6, wherein said biological sample is urine sample.

8. The ELISA method of claim 7, wherein the determined CYP 1A2 phenotype of said individual allows a physician to predict susceptibility to carcinogen induced diseases and/or to individualize drug treatments.

9. A competitive enzyme linked immunosorbent assay (ELISA) kit for determining CYP 1A2 phenotype, which comprises at least three antibodies each specific to caffeine or a different metabolite of caffeine to measure their molar ratio in biological sample of an individual after drinking a caffeine solution; wherein a molar ratio of 4 is indicative of slow intermediate and of 12 is indicative of fast CYP 1A2 metabolizers; and whereby said molar ratio is indicative of a CYP 1A2 phenotype of said individual.

10. The competitive ELISA kit of claim 9, further comprises:

a) a plate coated with a first antibody specific to caffeine;

b) a second antibody specific to a first metabolite of caffeine;

c) a third antibody specific to a second metabolite of caffeine;

d) a known amount of caffeine-horseradish peroxidase conjugate wherein a standard calibration curve is obtained;

e) a known amount of 1,7-dimethyl xanthine-horseradish peroxidase conjugate wherein a standard calibration curve is obtained; and

f) a known amount of 1,7-dimethyluric acid-horseradish peroxidase conjugate wherein a standard calibration curve is obtained.

11. The method of claim 1 wherein said specific antibodies are polyclonal or monoclonal antibodies.

80. The competitive ELISA kit of claim 74 wherein said specific antibodies are polyclonal antibodies.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : G01N 33/53

A2

(11) International Publication Number: WO 00/55624

(43) International Publication Date: 21 September 2000 (21.09.00)

(21) International Application Number: PCT/CA00/00246

(22) International Filing Date: 9 March 2000 (09.03.00)

(30) Priority Data:
60/124,488 15 March 1999 (15.03.99) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ELISA KIT FOR THE DETERMINATION OF METABOLIC PHENOTYPES

(57) Abstract

The invention relates to an enzyme linked immunosorbent assay (ELISA) kit for the rapid determination of metabolic phenotypes including but not limited to CYP 1A2, N-acetyltamferase-1 (NAT-1), CYP 2P6, CYP 2E1 and CYP 3A4, which can be used on a routine basis in a clinical laboratory. The ELISA kit allows physicians to a) individualize therapy of drugs such as theophylline, tamoxifen, and clozapine and b) to predict susceptibility to carcinogen induced diseases such as colon rectal cancers. To reduce the number of patients undergoing clinical testing by selecting for patients with the appropriate phenotype most likely to respond.

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INTERNATIONAL SEARCH REPORT

In Application No
PCT/CA 00/00246

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/53 G01N33/543 C07D473/08 C07D473/10 C07D473/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WONG P ET AL: "Synthesis of caffeine metabolites derivatives for measuring CYP1A3 activity by ELISA." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 53 XP002144104 90th Annual Meeting of the American Association for Cancer Research;Philadelphia, Pennsylvania, USA; April 10-14, 1999, March, 1999 ISSN: 0197-016X abstract --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2000	13. 11. 00

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 04757 A (UNIV TEXAS) 16 February 1995 (1995-02-16) page 5, line 7-13 page 5, line 29 -page 6, line 13 page 9, line 9-29 page 11, line 17-23 page 12, line 5-15 claims 9,11,13,14,16,18-29,37	1-16
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1991 TANG B-K ET AL: "CAFFEINE AS A METABOLIC PROBE VALIDATION OF ITS USE FOR ACETYLATOR PHENOTYPING" Database accession no. PREV199192067910 XP002144105 cited in the application abstract & CLINICAL PHARMACOLOGY & THERAPEUTICS, vol. 49, no. 6, 1991, pages 648-657, ISSN: 0009-9236	1-16
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1990 KILBANE A J ET AL: "HUMAN N-ACETYLATION GENOTYPE DETERMINATION WITH URINARY CAFFEINE METABOLITES" Database accession no. PREV199090015389 XP002144106 cited in the application abstract & CLINICAL PHARMACOLOGY & THERAPEUTICS, vol. 47, no. 4, 1990, pages 470-477, ISSN: 0009-9236	1-16
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1998 (1998-05) MEACHER DIANNE M ET AL: "Analysis of NAT and CYPIA2 phenotypes and NAT2* genotype by capillary electrophoresis." Database accession no. PREV199800360878 XP002144107 cited in the application abstract & BIOMARKERS, vol. 3, no. 3, May 1998 (1998-05), pages 205-218, ISSN: 1354-750X	1-16

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INTERNATIONAL SEARCH REPORT

Ir [redacted] Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 645 459 A (COOK DORN C ;PARKINSON ANDREW (US)) 29 March 1995 (1995-03-29) page 3, line 6,7 page 3, line 48 -page 4, line 55 claims 1-5 ---	1-16
A	US 5 830 672 A (LEYLAND-JONES BRIAN ET AL) 3 November 1998 (1998-11-03) column 2, line 28-50 column 3, line 42-55 example 1 claim 5 -----	1-16

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INTERNATIONAL SEARCH REPORT

nal application No.
PCT/CA 00/00246

Box I Observati ns where certain claims were found unsearchabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in r spect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
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Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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1 - 16

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 - 16

   Method, ELISA and kit for determining CYP 1A2 phenotype, based on the determination of the molar ratio between caffeine and selected metabolites thereof.

2. Claims: 17 - 32

   Method, ELISA and kit for determining NAT1 phenotype, based on the determination of the molar ratio between p-aminosalicylic acid and selected metabolites thereof.

3. Claims: 33 - 48

   Method, ELISA and kit for determining CYP 2D6 phenotype, based on the determination of the molar ratio between dextromethorphan and selected metabolites thereof.

4. Claims: 49 - 64

   Method, ELISA and kit for determining CYP 2E1 phenotype, based on the determination of the molar ratio between chlorzoxazone and selected metabolites thereof.

5. Claims: 65 - 80

   Method, ELISA and kit for determining CYP 3A4 phenotype, based on the determination of the molar ratio between dextromethorphan and selected metabolites thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir Application No
PCT/CA 00/00246

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